The effects of the national HPV vaccination programme in England, UK, on cervical cancer and grade 3 cervical intraepithelial neoplasia incidence: a register-based observational study

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Summary

Background

Human papillomavirus (HPV) immunization with the bivalent vaccine (Cervarix) was introduced in England in 2008: routine vaccination was offered to 12-13-year-old (school year 8) girls with “catch-up” for females aged 14-18 in 2008/10. The aim of our study is to quantify the early impact of this immunization programme on cervical cancer and cervical carcinoma in situ (CIN3) registrations.

Methods

We used a modified age-period-cohort Poisson regression model to estimate the relative risk of cervical cancer in three vaccinated cohorts compared with earlier cohorts that just missed out on HPV vaccination. The three “vaccinated” cohorts (with a total of 13·7 million-years of follow-up aged 20 to <30 years) allowed to account for differences in the school year in which the vaccine was offered and its national coverage. Adjustment for confounding was made using information on changes in cervical screening policy and historical events that impacted on cervical cancer incidence. Results were compared across models with different adjustments for confounders.

Findings

The estimated relative reduction in cervical cancer rates was 34% (95% confidence interval [CI]: 25% to 41%) in those offered the vaccine in school years 12-13, 62% (95% CI: 52% to 71%) for school year 10-11 and 87% (95% CI: 72% to 94%) for school year 8 compared with the reference unvaccinated cohort. The corresponding risk reductions for CIN3 were respectively 39%, 75% and 97%. These results differed little across models. We estimate that by June 2019 there had been 448 (95% CI: 339 to 556) fewer than expected cervical cancers and 17,235 (95% CI: 15,919 to 18,552) fewer than expected CIN3 in vaccinated cohorts in England.

Interpretation

We observed a substantial reduction in cervical cancer and CIN3 in younger women after the introduction of HPV immunization in England, especially in those who were offered the vaccine at age 12-13 years.

Funding

Cancer Research UK.

Research in context

Evidence before this study

Both randomised controlled trials and surveillance studies have shown the usefulness of HPV vaccination at preventing HPV infection and cervical intraepithelial neoplasia (CIN), but direct evidence of its effect on cervical cancer incidence is limited. Preliminary evidence that it protects against HPV-associated cancers was provided by a combined passive follow-up of women participating in two Finnish vaccination trials (one using the quadrivalent and the other the bivalent vaccine) compared with an unvaccinated cohort, but the number of cancers was too small to estimate efficacy with precision. A recent analysis of cervical cancer rates in Sweden showed reduced risk of cervical cancer in those who received Gardasil (quadrivalent HPV vaccine) but estimates of efficacy varied depending on the adjustments made.

Added value of this study

Our study provides the first direct evidence of the prevention of cervical cancer using Cervarix (bivalent HPV vaccine). We defined our cohorts to account for the age at which women were offered HPV immunization and the differences in national vaccination coverage. This allowed us to estimate the effect of the routine vaccination programme carried out in 12-13-year-old girls (school year 8) separately from the catch-up campaigns that targeted older girls in school years 10-11 and 12-13 who might have already been exposed to HPV before vaccination and for whom coverage was lower.

Implications of all the available evidence

Our findings add evidence to the very limited literature showing that national HPV immunization programmes can lead to a substantial reduction in cervical cancer incidence, especially if the vaccination coverage is high and women are offered the vaccine at a younger age. Although it is still too early to assess the full impact of the English vaccination programme, our results should contribute towards a better understanding and recognition of the benefits of HPV immunization.

Introduction

Human Papillomavirus (HPV) vaccination has been introduced in over 100 countries and underlies the WHO's global strategy for the elimination of cervical cancer.[1,2] In 2019 the global market volume for vaccines against HPV infections reached approximately 41·4 million doses, with the bivalent one having an estimated market share by volume of around 23%.[3] Vaccines have been shown in randomised controlled trials to prevent type-specific HPV infections and cervical intraepithelial neoplasia in HPV-naïve cohorts, but there is a lack of high-quality empirical evidence regarding their impact on cervical cancer incidence.

HPV immunization was introduced in England in September 2008 using the bivalent HPV vaccine (Cervarix). The goal was to reduce cervical cancer incidence by preventing persistent infections from the two most common high-risk types of HPV (16 and 18), which are responsible for approximately 80% of all cervical cancers in the UK.[4] Since the HPV vaccine is most effective when given prior to any exposure to HPV viruses, i.e. before sexual activity starts, routine vaccination was offered to 12-13-year-old (school year 8)[1] girls. A "catch up" was offered to girls aged 17-18 (born September 1990-August 1991) in 2008/09 and those aged 14-18 (born September 1991-August 1995) in 2009/10. Annual three-dose HPV immunization coverage between 2008/09 and 2011/12 was very high for those in school year 8 (80·9-88·0%) but lower for the catch-up cohorts (70·8-75·7% for school years 10-11 and 38·9-48·1% for school years 12-13).[5-7] The bivalent vaccine was replaced by the quadrivalent vaccine, Gardasil, in September 2012.

By ten years after the introduction of the HPV vaccination in England there had been substantial declines in HPV 16/18 and HPV 31/33/45 infections among 16 to 24-year-old women undergoing chlamydia screening.[8] In Scotland a dramatic reduction in preinvasive cervical disease has been seen in women aged 20.[9] Early modelling suggested that HPV vaccination would have no discernible impact of cervical cancer rates for at least eight years after vaccination but that there would be substantial impact on rates in women aged 20-29 by the end of 2019.[10] Recently, analysis of cervical cancer rates in Swedish women who did and did not receive the quadrivalent

[1] School year 8 in England corresponds to 7th grade in the US education system. In England students are 12 years of age at the start of year 8 and turn 13 during the school year.

vaccine (Gardasil) showed reduced risk of cervical cancer but the magnitude of the effect was dependent on adjustments made for confounders.[11]

It has now been over ten years since England introduced HPV immunization. Although it is still premature to assess the full impact of the programme, we can now investigate its early effects on the incidence of cervical cancer. Others have shown the impact of HPV vaccination on HPV infection and cervical intraepithelial neoplasia (CIN) rates, [8,12] but the only direct evidence of its effect on cervical cancer relates to the quadrivalent vaccine.[11]

Here we used population-based cancer registry data to estimate the early impact of the HPV immunization programme (using Cervarix) on cervical cancer and, separately, cervical carcinoma in situ (CIN3) rates in England.

Methods

The individual-level relationship between being vaccinated and cervical cancer incidence is likely to be confounded by largely unmeasurable variables related to beliefs, behaviours, and lifestyle. By contrast, the relation between the offer of vaccination and cervical cancer diagnosis is confounded by age, calendar time and birth cohort (which determines whether or not women would have been offered HPV vaccination and also when they are first invited for cervical screening) but is independent of factors such as beliefs and lifestyle. We defined three “vaccinated” cohorts to account for the school year in which the vaccine was offered (12-13, 10-11, 8) and differences in the vaccination coverage.

In the absence of herd immunity and cross-protection against HPV types other than 16 and 18, the HPV vaccination programme would be expected to reduce cervical cancer rates by an amount roughly equal to the product between 80% (i.e. the approximate percentage of cervical cancers caused in England by HPV 16/18)[4] and the vaccine coverage. Using this approximation, we obtain a lower limit of expected effectiveness by assuming that any fewer than 3 doses provides no protection and an upper limit by assuming 100% efficacy (against disease caused by HPV 16/18) from a single dose. The expected reduction in cervical cancer incidence would then be around 36%-48%, 59%-64% and 68%-71% in the cohorts offered vaccination in school years 12-13, 10-11 and 8, respectively.

One might anticipate the risk reduction in these last two groups to be larger due to: herd immunity, partial cross-protection or a higher prevalence of HPV 16/18 among those diagnosed at a younger age. By contrast, early vaccine effectiveness in women vaccinated at later ages will be lower as many of those who would develop cervical cancer in their 20s would have been infected before vaccination.

Data

Data on cervical cancer (ICD10 C53) and CIN3 (ICD10 D06) diagnosed between January 2006 and June 2019 in women aged 20 to 64 years and resident in England were extracted on 26th January 2021 from the dataset produced by the National Cancer Registration and Analysis Service (NCRAS),[13] Public Health England (PHE). Mid-year population estimates were obtained from the Office for National Statistics.[14]

Statistical analysis

We used an extension of the age-period-cohort (APC) Poisson model[15,16] to estimate the effect of HPV vaccination on incidence rates of cervical cancer and, separately, CIN3. In addition to the usual functions of age, period, and cohort, we included age-by-cohort and age-by-period interactions to handle historical events known to have an impact on cervical cancer incidence. Cancer cases were aggregated by months of age, period and cohort and the corresponding population estimates (person-time) were included after a logarithmic transformation as an offset; 95% confidence intervals used robust standard errors.[17,18] Models included a combination of the following covariates.

Main age effects

We considered seven age groups: 20 to <24·5, 24·5 to <26, 26 to <30, 30 to <35, 35 to <45, 45 to <55, and 55 to <65 years. In particular, the cut-off point of 24.5 years was included to account for the dramatic increase in cancer diagnosis in the months following the first invitation to screening[19] and the fact that since 2012 women have received their first invitation at age 24.5 years. Older age groups were retained in the analysis so that we could capture trends in CIN3 and cervical cancer diagnosis and registration over time. This was useful for estimation of historical events, seasonal variation in registrations and any under-registration due to inclusion of more recent

data. Sensitivity analyses were performed using restricted cubic splines.[20,21] Further details are provided in the supplementary material.

Main period effects

1. Linear trend in time (drift), centred on January 2016.
2. Four dummy variables to capture seasonal variations in diagnoses: January–March, April–June, July–September, and October–December.
3. Four dummy variables to adjust for possible under-registration of recent cancer diagnoses: January 2006–December 2017 (complete registration), January 2018–September 2018, October 2018–March 2019, April 2019–June 2019 (least complete registration).

Main cohort effects

We defined seven birth cohorts corresponding to differences in the age at first invitation to screening and the school years in which HPV vaccination was offered. Changes in age at first screening invitation greatly affect age-specific cancer rates.[19] In England the national cervical cancer screening programme was introduced in 1988 for women aged between 20 and 64 years. In 2004 the age of first invitation to screening was increased to 25 years. Since the new policy was implemented over a 15-month period commencing in August 2004, women born between September 1984 and October 1985 were first invited for screening either at age 20 or at age 25 years. In 2012 the age at first screening invitation changed once more, this time to 24.5 years. We therefore defined birth cohorts as follows (see Figure 1 for a schematic representation of these cohorts).

1. *Born before September 1984*: first screening invitation at age 20 years; no HPV vaccination.
2. *Born September 1984 – October 1985*: first screening invitation at either age 20 or 25 years; no HPV vaccination.
3. *Born November 1985 – April 1989*: first screening invitation at age 25 years; no HPV vaccination.
4. *Born May 1989 – August 1990*: first screening invitation at age 24·5 years; no HPV vaccination.
5. *Born September 1990 – August 1993*: offered HPV vaccination in school years 12 or 13 (aged 16-18 years); first screening invitation at age 24·5 years.

6. *Born September 1993 – August 1995*: offered HPV vaccination in school years 10 or 11 (aged 14-16 years) and first screening invitation at age 24·5 years.
7. *Born in or after September 1995*: offered routine HPV immunization in school year 8 (age 12-13 years); not invited to screening before age 24·5 years.

Age-by-period interactions

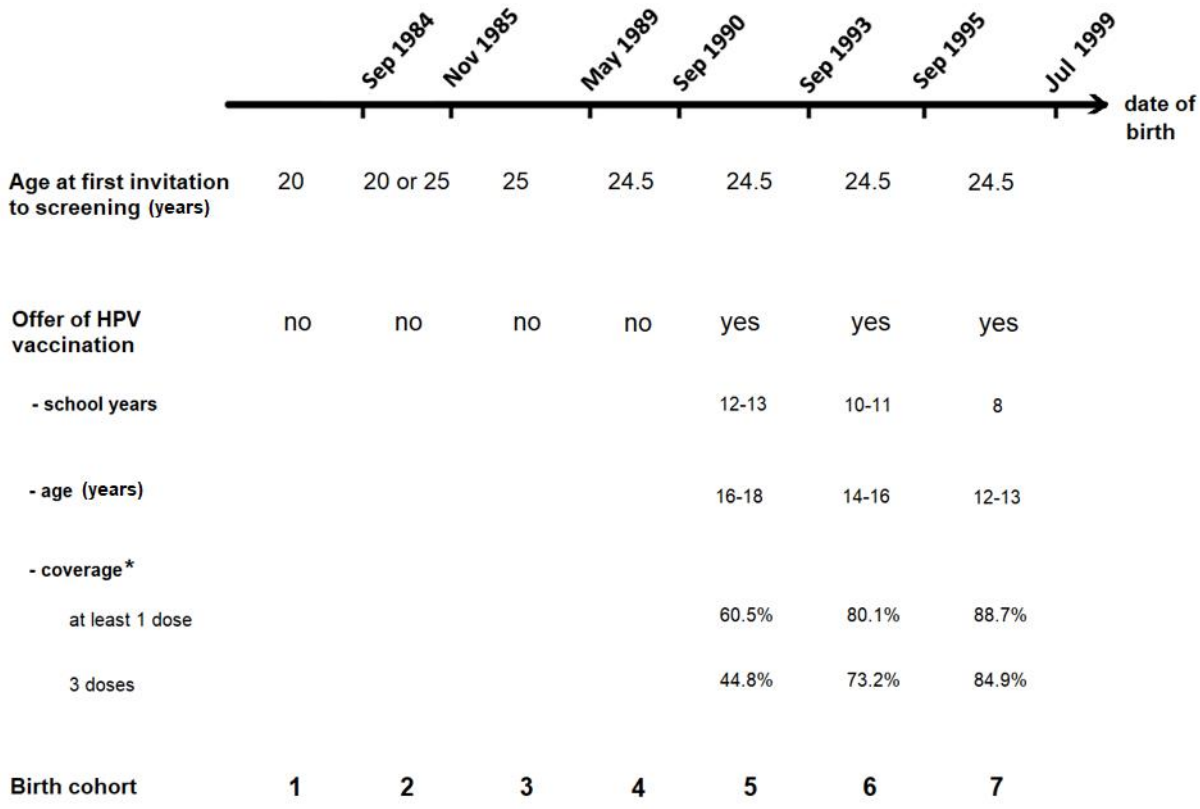
1. Dummy variable for women aged 20 to <50 years between January and June 2009 to account for the increase in cervical screening from the so-called Jade Goody effect.[22]
2. Dummy variable for women aged 24·5 years and above between March and June 2019 to account for the expected increase in incidence due to the cervical screening awareness campaign launched in March 2019 by PHE.[23]

Age-by-cohort interactions

We included a set of dummy variables to account for increased diagnosis of prevalent cancer cases arising from policy changes in the age of first invitation to screening.[19] We assumed that an invitation for first screening increases cancer detection substantially for six months and to a lesser extent for a further six months. Specifically, we considered dummy variables for the following cohort- and age-related groups:

1. women in cohort 2 aged 25 to <25·5 years
2. women in cohort 2 aged 25·5 to <26 years
3. women in cohort 3 aged 25 to <25·5 years
4. women in cohort 3 aged 25·5 to <26 years
5. women in cohorts 4-7 aged 24·5 to <25 years
6. women in cohorts 4-7 aged 25 to <25·5 years

The purpose of these six dummy variables is therefore to capture the increase in diagnoses made within 6 months and 6-12 months of a first invitation to cervical screening.



* Vaccine coverages include (when data are available) mop-up vaccinations.

Figure 1: Definition and characteristics of the birth cohorts. The cohort-specific vaccination coverages were obtained by averaging the relevant national coverages reported in the literature or the web (see Table S1 in the supplementary appendix for more details).

Modelling strategy

Working from a statistical analysis plan, analysis code was written before the authors had access to the data. After testing on simulated data consisting of artificial cancer records, the code was sent to PHE for running on the real data and the results were shared. Analysis code was subsequently revised and run on a later data extract. We present both the findings of the original (blinded) model and those of the subsequent models (revised after seeing the results of modelling on a preliminary data extract).

The main analysis considered three models that differ only in terms of adjustments made for under-registration and the PHE's awareness campaign.

Model 1: All main effects for age and cohort, age-by-cohort interactions, linear trend (drift), dummy variables for the Jade Goody effect and seasonal effects.

Model 2 (adjustment for under-registration): model 1 but with additional dummy variables for possible under-registration. This is the model we planned to use before we saw any of the data.

Model 3 (adjustment for the awareness campaign)*:* model 1 but with an additional age-by-period dummy variable for the PHE's awareness campaign.

Using each of these models, we estimated the number of cancers and CIN3 averted since the start of the HPV vaccination programme. This was done by comparing the expected number of events in the vaccinated cohorts (with different effects for each cohort) with the corresponding expected numbers when the cohort effects were forced to be the same as in the last unvaccinated cohort (i.e. the reference group). The point estimates and 95% confidence intervals were derived using the *margins* command in Stata.

Sensitivity analyses

For CIN3, we also fitted models to the sub-sample of women aged 24·5 years and over as CIN3 is diagnosed almost exclusively through screening and rates of CIN3 in women aged 20-24·5 decreased dramatically as screening in this age group was phased out. Additional sensitivity analyses evaluated the robustness of our models, e.g. by changing the number and location of the cubic spline knots.

All analyses were performed using Stata version 16·1.[24]

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

During the study period there were 27,946 diagnoses of cervical cancer and 318,058 of CIN3 (Table 1). The study included a total of 13·7 million-years of follow-up aged 20 to <30 years in the three "vaccinated" cohorts.

The crude incidence rates per 100,000 women-years (Table 2) were particularly low for women offered the vaccine at age 12-13 years (0·3 for cervical cancer and 2·0 for CIN3). We also noticed that, as reported previously,[19] crude incidence rates for age 24·5 to <26 in cohorts 2 to 4 were much higher than in cohort 1, reflecting changes in age at first screening invitation. This is also shown in the highly significant age-by-cohort interaction terms (see Tables S2-S4 in supplementary appendix).

The estimated cohort-specific incidence rate ratios (IRRs) changed very little across the three models (Table 3), all of which adjusted for confounding by age and period but differed in whether they explicitly allowed for under-registration in recent months or the impact of a campaign to increase screening participation. For simplicity of presentation, we report results from model 3. Incidence rates of invasive cervical cancer were estimated to be 34% (95% CI: 25% to 41%) lower in cohort 5 (vaccine offered in school years 12-13), 62% (95% CI: 52% to 71%) lower in cohort 6 (vaccine offered in school years 10-11) and 87% (95% CI: 72% to 94%) lower in cohort 7 (vaccine offered in school year 8) compared with the unvaccinated cohort 4. The corresponding effectiveness of the vaccination programme in preventing CIN3 was 39% (95% CI: 36% to 41%) lower in cohort 5, 75% (95% CI: 72% to 77%) lower in cohort 6 and 97% (95% CI: 96% to 98%) lower in cohort 7.

When for CIN3, as part of our sensitivity analysis, we excluded women aged 20-24·5 (it is no longer possible to estimate effects for cohort 7) the estimated incidence rates for cohorts 5 and 6 were respectively 35% (down from 39%) and 66% (down from 75%) lower than that for cohort 4 (Table S4). The overall difference between the vaccinated cohorts 5 to 7 and the unvaccinated cohort 4 was highly significant ($p<0·001$) in all models for both cervical cancer and CIN3. This was the case also when we tested the joint effect of cohorts 5 and 6 versus cohort 4 in women with CIN3 aged 24·5 years and over.

In our sensitivity analyses the ranges of the estimated IRRs for cohorts 5, 6 and 7 (relative to cohort 4) were respectively 0·66-0·69, 0·32-0·40 and 0·12-0·30 for cervical cancer and 0·60-0·61, 0·21-0·27 and 0·03-0·07 for CIN3 (Table S5). The greater

variability observed in the results for cohort 7 is expected since women in that cohort were at most aged 24.5 years in March 2019 and diagnosis of cervical cancer is rare in such young women.

Model 2 (Tables S2 and S3) showed no evidence of under-registration. The estimated IRRs for the two most recent period intervals (October 2018–March 2019 and April 2019–June 2019) compared with January 2006–December 2017 were significantly above 1 for both cervical cancer (IRR=1·13 [95% CI: 1·06 to 1·21] and IRR=1·20 [95% CI: 1·09 to 1·31], respectively) and CIN3 (IRR=1·14 [95% CI: 1·10 to 1·17] and IRR=1·24 [95% CI: 1·20 to 1·29], respectively). The increased number of diagnoses registered in those two period intervals are most likely due to the significant rise in screening uptake following the PHE's awareness campaign launched in 2019 (see the results for Model 3 in Tables S2 and S3).

Figure 2 shows the Model-3 estimates of cumulative incidence for age 20 to <30 years for cohorts 4 to 7. Models 1 and 2 gave similar estimates (Table S6).

From Model 3 we estimated that by June 2019 there had been 448 (95% CI: 339 to 556) fewer cervical cancers and 17,235 (95% CI: 15,919 to 18,552) fewer CIN3 in vaccinated cohorts in England than would have been expected had the cohort effects been the same as in the most recent unvaccinated cohort. The corresponding numbers of cancers and CIN3 prevented under models 1 and 2 are presented in Table S7.

Table 1: characteristics of the cervical cancer and CIN3 cases included in our study.

	Invasive cervical cancer	CIN3	Women-years in population (millions)
Total	27,946	318,058	214·8
Birth cohort			
1: invited from age 20 years and unvaccinated	23,665	205,291	175·5
2: invited from age 20 or 25 years and unvaccinated	930	20,723	5·7
3: invited from age 25 years and unvaccinated	2,150	56,103	15.2
4: invited from age 24·5 years and unvaccinated	563	17,279	4·6
5: invited from age 24·5 years and offered vaccine in school years 12-13	561	16,959	8·0
6: invited from age 24·5 years and offered vaccine in school years 10-11	70	1,654	3·3
7: not invited before age 24·5 years and offered vaccine in school year 8	7	49	2·5
Age at diagnosis (years)			
20 to <24·5	329	9,886	20·9
24·5 to <26	1,579	57,938	7·5
26 to <30	3,360	88,606	19·7
30 to <65	22,678	161,628	166·7
Year of diagnosis			
2006-2010	9,893	118,851	77·9
2011-2015	10,433	125,168	79·9
2016	2,124	21,979	16·2
2017	2,124	20,917	16·3
2018	2,185	20,245	16·3
Jan-Jun 2019	1,187	10,898	8·2

Table 2: Crude incidence rates per 100,000 women-years by cohort and age group (for simplicity, restricted to age<30 years) for invasive cervical cancer and CIN3. Number of cases are reported between brackets.

	Rates per 100,000 women-years (Number)					
	Invasive cervical cancer			**CIN3**		
	age group			*age group*		
	20 to <24·5	*24·5 to <26*	*26 to <30*	*20 to <24·5*	*24·5 to <26*	*26 to <30*
Unvaccinated cohorts						
cohort 1: invited from age 20 years and no vaccine	4·2 (70)	11·7 (246)	16·1 (1,532)	233·8 (3,893)	498·3 (10,522)	446·9 (42,443)
cohort 2: invited from age 20 or 25 years and no vaccine	2·5 (38)	27·0 (176)	20·4 (352)	100·6 (1,504)	847·3 (5,520)	489·0 (8,443)
cohort 3: invited from age 25 years and no vaccine	2·0 (109)	28·2 (557)	18·8 (987)	52·9 (2,868)	1,027·6 (20,298)	476·4 (25,020)
cohort 4: invited from age 24·5 years and no vaccine	1·8 (37)	27·8 (211)	18·0 (315)	29·9 (629)	1,141·7 (8,680)	452·9 (7,948)
Vaccinated cohorts						
cohort 5: invited from age 24·5 years and offered vaccine in school years 12-13	1·0 (47)	20·0 (340)	11·5 (174)	15·9 (755)	673·2 (11,452)	312·8 (4,752)
cohort 6: invited from age 24·5 years and offered vaccine in school years 10-11	0·7 (21)	14·5 (49)	..	6·3 (188)	434·9 (1,466)	..
cohort 7: not invited before age 24·5 years and offered vaccine in school year 8	0·3 (7)	..	..	2·0 (49)	..	..

Table 3: estimated incidence rate ratios (IRRs) and 95% confidence intervals (CIs) of either invasive cervical cancer or CIN3 among the vaccinated and unvaccinated birth cohorts. The estimates are adjusted for the covariates included in the models (see methods).

	Invasive cervical cancer			**CIN3**		
	Model 1	**Model 2** (under-registration)	**Model 3** (campaign)	**Model 1**	**Model 2** (under-registration)	**Model 3** (campaign)
	IRR (95% CI)	**IRR** (95% CI)	**IRR** (95% CI)	**IRR** (95% CI)	**IRR** (95% CI)	**IRR** (95% CI)
Unvaccinated cohorts						
cohort 1: invited from age 20 years and no vaccine	**0·99** (0·89, 1·10)	**1·00** (0·90, 1·11)	**0·99** (0·89, 1·10)	**0·97** (0·93, 1·00)	**0·98** (0·94, 1·01)	**0·97** (0·94, 1·01)
cohort 2: invited from age 20 or 25 years and no vaccine	**1·08** (0·95, 1·22)	**1·09** (0·97, 1·23)	**1·08** (0·96, 1·22)	**1·02** (0·98, 1·06)	**1·03** (0·99, 1·07)	**1·03** (0·99, 1·06)
cohort 3: invited from age 25 years and no vaccine	**1·03** (0·93, 1·15)	**1·04** (0·94, 1·16)	**1·04** (0·93, 1·15)	**1·01** (0·97, 1·04)	**1·02** (0·98, 1·05)	**1·01** (0·98, 1·05)
cohort 4: invited from age 24·5 years and no vaccine **(reference category)**	**1·00**	**1·00**	**1·00**	**1·00**	**1·00**	**1·00**
Vaccinated cohorts						
cohort 5: invited from age 24·5 years and offered vaccine in school years 12-13	**0·67** (0·59, 0·75)	**0·66** (0·58, 0·74)	**0·66** (0·59, 0·75)	**0·61** (0·59, 0·64)	**0·61** (0·58, 0·64)	**0·61** (0·59, 0·64)
cohort 6: invited from age 24·5 years and offered vaccine in school years 10-11	**0·39** (0·31, 0·50)	**0·37** (0·29, 0·47)	**0·38** (0·29, 0·48)	**0·26** (0·24, 0·29)	**0·24** (0·22, 0·27)	**0·25** (0·23, 0·28)
cohort 7: not invited before age 24·5 years and offered vaccine in school year 8	**0·13** (0·06, 0·27)	**0·12** (0·06, 0·26)	**0·13** (0·06, 0·28)	**0·03** (0·02, 0·04)	**0·03** (0·02, 0·04)	**0·03** (0·02, 0·04)

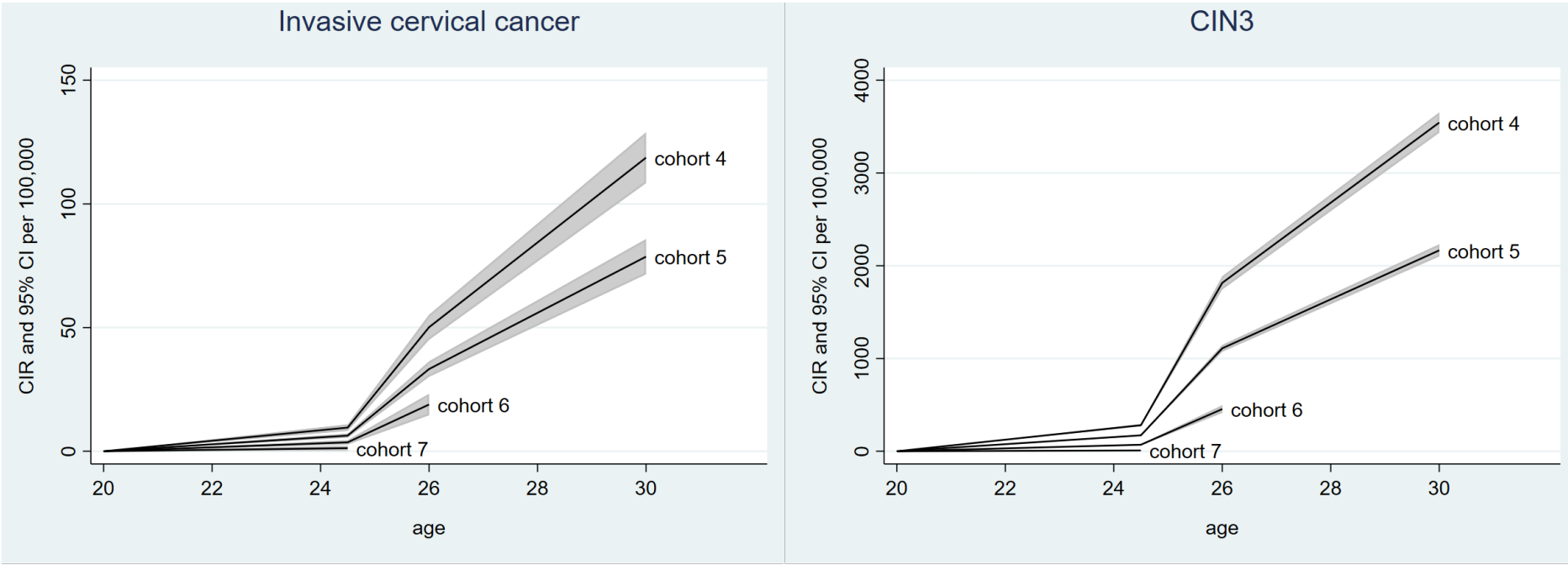


Figure 2: Cumulative incidence rates (CIRs) and 95% confidence intervals (CIs) per 100,000 for cohort 4 to 7 obtained from Model 3 for age between 20 and <30 years. Risk estimates were obtained with all other covariates fixed at their reference values (with the period effect corresponding to January 2016). Solid lines represent estimated CIRs, while shaded areas denote the 95% CIs.

Discussion

The introduction of national HPV immunization programmes represents an important step forward in cervical cancer prevention. To the best of our knowledge, our study provides the first direct evidence of the impact of HPV vaccination using Cervarix on cervical cancer incidence. We find a large reduction in cervical cancer rates in all three "vaccinated" cohorts and especially in those who were offered the vaccine in school year 8 (aged 12-13 years). The success of vaccination programmes relies not only on the efficacy of the vaccine but also on the proportion of the population vaccinated. There is growing evidence[25-28] that a single dose of HPV vaccine provides good protection against persistent infection with efficacy similar to that of three doses. Sankaranarayanan and colleagues (2016) showed that the short-term protection from one dose of the quadrivalent HPV vaccine is similar to that from two or three doses, stressing that this merits further investigation.[29] Analogous findings have been reported for the bivalent vaccine.[30]

HPV one-dose coverage in England between 2008/09 and 2011/12 ranged between 85·9% and 90·6% in the routine cohorts (cohort 7) and between 55·6% and 81·9% in the catch-up cohorts.[6,7] It has remained high afterwards until the COVID-19 pandemic impacted on uptake in the 2019/20 academic year.[31] Additionally, unvaccinated women in the vaccinated cohorts are likely to benefit from the indirect protection (herd immunity) of the vaccination programme. Empirical evidence suggesting herd immunity for HPV 16 and 18 and cross-protection against HPV 31, 33 and 45 was, for example, reported in Scotland after the introduction of their HPV immunization programme.[9] It is worth noting that substantial herd immunity is much more easily attainable for sexually transmitted infections like HPV than for airborne diseases.[32]

In our study whether or not women (living in England at the time) would have been offered HPV vaccination depends only on their birth cohort and this is unrelated with unobserved factors such as lifestyle and behaviour. There is still confounding by age and period (and interactions of them) but, since they are observed, they can be handled by careful modelling. The incidence of cervical cancer varies rapidly with age and is affected by screen-detected cancers, particularly on first screen. The precise age of first screen and screening uptake changes over time. Even small alterations to cervical screening (or the reporting of cervical histology) or cancer registration could have substantial impact on trends in registered CIN3 in women in their 20s. Analysing

published data based on incidence in 5-year age groups and calendar year of diagnosis would lead to a mix of vaccinated and unvaccinated cohorts in any one age group and this would mask any effect of vaccination. Changes in vaccine uptake by age and the higher likelihood of pre-existing infection at the time of vaccination in women who go on to develop cervical cancers at relatively young ages are likely to modify the expected impact of vaccination, particularly in the catch-up cohorts. We therefore defined our cohorts to account for both the age at which women were offered HPV immunization and the differences in achieved vaccination coverage. This allowed us to estimate the effect of the routine vaccination programme carried out in 12-13-year-old girls (school year 8) separately from the catch-up campaigns that targeted older girls in school years 10-11 and 12-13 who might have already been exposed to HPV before vaccination. Careful modelling was required to accurately define the different birth cohorts and to adjust for changes to cervical screening and possible secular trends in cervical cancer at all ages before assessing the impact of vaccination.

From previous research[19,22] we have detailed information on the impact that policy changes of age at first screening and particular events (e.g. the death of Jade Goody) had on cervical cancer incidence, so in our regression models we made careful adjustment for this confounding. The cohort effect that we attribute to the offer and uptake of HPV vaccination could mirror changes in the underlying incidence of sexually transmitted infections, but national data on chlamydia, gonorrhoea and genital herpes in young women between 2010 and 2019 do not show any strong decreasing trends.[33] Thus, we argue that our findings provide an unbiased estimate of the population-level effect of bivalent HPV vaccination (at different ages and with different levels of coverage) on subsequent cervical cancer rates.

Preliminary evidence that HPV vaccination protects against HPV-associated cancer was provided by a Finnish study that analysed data from passive follow-up of two randomised control trials of vaccine efficacy with a comparison cohort of unvaccinated women.[34] However, women did not all receive the same vaccine (some were vaccinated with Cervarix and others with Gardasil) and the number of cancers was too small to estimate efficacy with precision.

Our study has some limitations, the key one being that individual-level data on vaccination status were not available so we could not estimate individual-level efficacy. Additionally, we have no information on the HPV type in each of the cancers.

As an observational study of routinely collected cancer registry records, there is a risk that the relationship between the offer of the HPV vaccine and subsequent diagnosis of cervical cancer is confounded by factors not accounted for in the analysis. However, as mentioned earlier, detailed information on changes in cervical screening policy and historical events that had an impact on cervical cancer incidence were available and allowed us to make careful adjustment for these known confounding factors. The other main limitation is the relatively small numbers of cancers expected (in the absence of vaccination) in the "vaccinated" cohorts. This is most extreme for the group vaccinated aged 12-13 years for whom the expected number of cancers was under 60. Furthermore, since most of the follow-up for women in cohort 6 is whilst they are under age 25 years, most of their cancers (and virtually all the CIN3) will have been screen-detected and so small differences in the exact age of first screening can have a big effect on the numbers of registered cases aged under 25 years. The adjusted IRRs of CIN3 for cohort 6 may be artefactually low due to decreased screening under age 24·75 years (even a 3-month delay in screening could have a big impact on the results for this cohort). We also note that the incidence rate ratios in Table 3 are lower for CIN3 than they are for cervical cancer (particularly so for cohorts 6 and 7). This is a somewhat surprising finding as the proportion of CIN3 due to HPV16/18 is less than the proportion of cervical cancer that is due to these HPV types. It may be an artefact, but it warrants further investigation (including typing of CIN3 in younger women).

In our investigation the risk reductions of cervical cancer expected in the catch-up cohorts (cohorts 5 and 6) under a scenario requiring three doses and assuming no cross-protection and no herd immunity (i.e. 36% and 59%) fall well within our 95% confidence intervals. However, the magnitude of the reduction in those offered the vaccine in school year 8 (87% for cancer and 97% for CIN3) was much greater than would be expected (68%) under that scenario and also than would be expected assuming a single dose provides 100% protection against HPV 16 and 18 (71%). Mesher et al.[4] found that in the UK the prevalence of HPV16/18 was particularly high (92.9% [95% CI: 85.6% to 97.0%]) among women diagnosed with cervical cancer before age 30. This could at least in part explain the magnitude of the reduction among those offered the vaccine in school year 8. Nevertheless, our results (especially those for CIN3) might also be explained by herd protection in unvaccinated women within vaccinated cohorts and/or cross-protection against HPV infections other than 16 and

18 as shown for type-specific HPV infection.[12] In any case our findings should greatly reassure those still hesitant about the benefits of the HPV vaccination.

Acknowledgments

This work uses data that have been provided by patients and collected by the NHS as part of their care and support. The data are collated, maintained and quality assured by the National Cancer Registration and Analysis Service, which is part of Public Health England (PHE). The authors are very grateful to Jennifer Lai (National Cancer Registration and Analysis Service, Public Health England) for her help with data extraction and running some Stata code on the real data set. PS, AC and MF are supported by Cancer Research UK [grant number C8162/A16892 to PS].

Authors' contributions:

PS and AC conceptualised the study and prepared the original study protocol, which was subsequently reviewed by KS, MC, JLB and LEB and revised by PS, AC and MF. PS and MF developed the statistical methodology. MF wrote and tested the Stata code (checked by PS) for the data analysis and drafted the manuscript. BN and LEB verified the integrity of the cancer registry data. BN extracted the data set and ran the Stata code on it. PS, AC and MF interpreted the results and revised the manuscript. KS, MC, JLB, BN and LEB critically reviewed the manuscript. All authors approved the final submitted version.

Data sharing

The cancer registry data used in this paper are held by the National Cancer Registration and Analysis Service (NCRAS), PHE. Access to the data can be requested under PHE's data access arrangements through the Office for Data Release (https://www.gov.uk/government/publications/accessing-public-health-england-data/about-the-phe-odr-and-accessing-data). Mid-year population estimates are freely downloadable from the ONS website (https://www.ons.gov.uk/).

Declaration of interests

None

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Appendix

Table S1: national vaccination coverages by date of birth and corresponding cohort-specific estimates.

Table S2: adjusted incidence rate ratios and 95% confidence intervals of invasive cervical cancer in women aged 20 to <65 years.

Table S3: adjusted incidence rate ratios and 95% confidence intervals of CIN3 in women aged 20 to <65 years.

Table S4: adjusted incidence rate ratios and 95% confidence intervals of CIN3 in women aged 24·5 to <65 years.

Table S5: adjusted estimates of cohort-specific incidence rate ratios obtained from models using restricted cubic splines or categories for the age variable.

Table S6: estimated cohort-specific cumulative incidence rates for birth cohorts 4-7 obtained using models 1-3.

Table S7: Number of cases and 95% confidence intervals that by June 2019 Models 1-3 estimate had been averted since the introduction of the HPV vaccination programme in England.

Table S1: national vaccination coverages by date of birth and corresponding cohort-specific estimates.

Cohort and date of birth	National vaccination coverage		Cohort-specific coverage*	
	At least 1 dose	3 doses	At least 1 dose	3 doses
Cohort 5			60.5%	44.8%
1 Sep 1990 - 31 Aug 1991	66.1%	47.4%		
1 Sep 1991 - 31 Aug 1992	55.6%	38.9%		
1 Sep 1992 - 31 Aug 1993	59.8%	48.1%		
Cohort 6			80.1%	73.2%
1 Sep 1993 - 31 Aug 1994	78.4%	70.8%		
1 Sep 1994 - 31 Aug 1995	81.9%	75.7%		
Cohort 7			88.7%	84.9%
1 Sep 1995 - 31 Aug 1996	89.4%	84.4%		
1 Sep 1996 - 31 Aug 1997	85.9%	80.9%		
1 Sep 1997 - 31 Aug 1998	88.9%	86.3%		
1 Sep 1998 - 30 Jun 1999	90.6%	88.0%		

* Cohort-specific estimates were obtained by averaging the relevant national vaccination coverages by birth cohort. Data on national vaccination coverage were retrieved from the literature or the web and included information on mop-up vaccinations when available. The main data sources were http://data.parliament.uk/DepositedPapers/Files/DEP2012-1386/PQ119371-3.pdf (Table 1, page 5) and https://researchonline.lshtm.ac.uk/id/eprint/4648679/1/EPH_PhD_Mesher_D.pdf (Table 4.3, page 89). The 3-dose national coverage for Sep 1997-Aug 1998 and Sep 1998-Jun 1999 were updated using the figures displayed in Figure 6 (page 21) of https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/774074/HPV_Vaccine_Coverage_in_England_200809_to_201314.pdf. All these web sites were last accessed on 24th March 2021.

Table S2: adjusted incidence rate ratios (IRRs) and 95% confidence intervals (CIs) of invasive cervical cancer in women aged 20 to <65 years.

	Model 1				Model 2				Model 3			
	IRR	**p**	**95% CI**		**IRR**	**p**	**95% CI**		**IRR**	**p**	**95% CI**	
Age (years)												
20 to <24·5	1·000				1·000				1·000			
24.5 to <26	6·336	<0·001	5·451	7·366	6·243	<0·001	5·372	7·256	6·284	<0·001	5·407	7·303
26 to <30	8·124	<0·001	7·177	9·197	8·033	<0·001	7·101	9·087	8·071	<0·001	7·133	9·133
30 to <35	8·880	<0·001	7·795	10·116	8·738	<0·001	7·678	9·945	8·800	<0·001	7·730	10·019
35 to <45	7·914	<0·001	6·936	9·030	7·783	<0·001	6·826	8·873	7·840	<0·001	6·875	8·941
45 to <55	5·348	<0·001	4·681	6·109	5·262	<0·001	4·610	6·006	5·300	<0·001	4·642	6·051
55 to <65	4·731	<0·001	4·138	5·410	4·652	<0·001	4·071	5·315	4·687	<0·001	4·101	5·357
Linear trend (drift)	1·009	<0·001	1·006	1·013	1·005	0·010	1·001	1·009	1·007	<0·001	1·004	1·011
Seasonality												
Jan-Mar	1·000				1·000				1·000			
Apr-June	1·021	0·213	0·988	1·055	1·018	0·316	0·984	1·053	1·012	0·473	0·979	1·046
July-Sept	1·005	0·768	0·971	1·040	1·014	0·427	0·980	1·050	1·010	0·567	0·976	1·045
Oct-Dec	1·025	0·155	0·991	1·060	1·028	0·119	0·993	1·064	1·031	0·084	0·996	1·066
Birth cohorts												
1: invited at age 20 years and no vaccine	0·987	0·816	0·888	1·098	0·999	0·986	0·898	1·111	0·994	0·906	0·893	1·105
2: invited at age 20 or 25 years and no vaccine	1·077	0·228	0·954	1·216	1·090	0·165	0·965	1·230	1·084	0·192	0·960	1·224
3: invited at age 25 years and no vaccine	1·032	0·562	0·928	1·147	1·040	0·464	0·936	1·157	1·037	0·507	0·932	1·153
4: invited at age 24·5 years and no vaccine	1·000				1·000				1·000			
5: invited at 24·5 years and school years 12-13	0·666	<0·001	0·590	0·752	0·658	<0·001	0·583	0·743	0·663	<0·001	0·587	0·748
6: invited at 24·5 years and school years 10-11	0·393	<0·001	0·306	0·504	0·367	<0·001	0·286	0·471	0·377	<0·001	0·294	0·483
7: not invited before age 24·5 and school year 8	0·129	<0·001	0·061	0·273	0·125	<0·001	0·059	0·264	0·131	<0·001	0·062	0·277
Jade Goody effect	1·315	<0·001	1·229	1·406	1·312	0·000	1·227	1·404	1·317	0·000	1·231	1·409
Age-by-cohort interactions												
CxA_25y_mixed_1	3·334	<0·001	2·677	4·153	3·333	<0·001	2·676	4·151	3·331	<0·001	2·675	4·149
CxA_25y_mixed_2	1·815	<0·001	1·407	2·343	1·818	<0·001	1·409	2·347	1·817	<0·001	1·408	2·345
CxA_25y_1	3·593	<0·001	3·077	4·195	3·637	<0·001	3·114	4·248	3·615	<0·001	3·095	4·221
CxA_25y_2	1·827	<0·001	1·528	2·184	1·852	<0·001	1·549	2·215	1·838	<0·001	1·538	2·198
CxA_24y5_1	2·462	<0·001	2·061	2·941	2·549	<0·001	2·132	3·048	2·509	<0·001	2·099	2·998
CxA_24y5_2	2·529	<0·001	2·114	3·027	2·605	<0·001	2·175	3·120	2·572	<0·001	2·148	3·079
Possible under-registration												
Jan 2006 - Dec 2017					1·000							
Jan 2018 - Sep 2018					1·035	0·236	0·978	1·095				
Oct 2018 - Mar 2019					1·130	<0·001	1·057	1·207				
Apr 2019 - Jun 2019					1·198	<0·001	1·091	1·315				
Awareness campaign									1·198	<0·001	1·107	1·297
Constant (baseline incidence rate)	2·14E-5	<0·001	1·86E-5	2·46E-5	2·10E-5	<0·001	1·83E-5	2·41E-5	2·12E-5	<0·001	1·85E-5	2·44E-5

Table S3: adjusted incidence rate ratios (IRRs) and 95% confidence intervals (CIs) of CIN3 in women aged 20 to <65 years.

	Model 1				Model 2				Model 3			
	IRR	**p**	**95% CI**		**IRR**	**p**	**95% CI**		**IRR**	**p**	**95% CI**	
Age (years)												
20 to <24·5	1·000				1·000				1·000			
24·5 to <26	7·408	<0·001	7·040	7·796	7·325	<0·001	6·959	7·710	7·354	<0·001	6·989	7·739
26 to <30	6·969	<0·001	6·698	7·250	6·904	<0·001	6·637	7·182	6·926	<0·001	6·658	7·204
30 to <35	4·366	<0·001	4·179	4·561	4·309	<0·001	4·125	4·501	4·329	<0·001	4·144	4·521
35 to <45	2·004	<0·001	1·915	2·098	1·979	<0·001	1·891	2·071	1·988	<0·001	1·900	2·080
45 to <55	0·628	<0·001	0·599	0·658	0·620	<0·001	0·591	0·650	0·623	<0·001	0·594	0·653
55 to <65	0·255	<0·001	0·242	0·268	0·252	<0·001	0·239	0·265	0·253	<0·001	0·240	0·266
Linear trend (drift)	0·995	<0·001	0·993	0·996	0·991	<0·001	0·990	0·993	0·993	<0·001	0·991	0·994
Seasonality												
Jan-Mar	1·000				1·000				1·000			
Apr-June	1·052	<0·001	1·037	1·066	1·047	<0·001	1·032	1·062	1·043	<0·001	1·028	1·058
July-Sept	1·038	<0·001	1·023	1·053	1·046	<0·001	1·030	1·061	1·043	<0·001	1·028	1·058
Oct-Dec	1·037	<0·001	1·022	1·052	1·037	<0·001	1·022	1·053	1·042	<0·001	1·027	1·058
Birth cohorts												
1: invited at age 20 years and no vaccine	0·965	0·041	0·933	0·999	0·977	0·182	0·944	1·011	0·973	0·112	0·940	1·006
2: invited at age 20 or 25 years and no vaccine	1·018	0·337	0·982	1·056	1·031	0·104	0·994	1·070	1·026	0·168	0·989	1·065
3: invited at age 25 years and no vaccine	1·005	0·764	0·973	1·039	1·018	0·287	0·985	1·052	1·013	0·428	0·980	1·048
4: invited at age 24·5 years and no vaccine	1·000				1·000				1·000			
5: invited at 24·5 years and school years 12-13	0·614	<0·001	0·588	0·641	0·609	<0·001	0·583	0·636	0·611	<0·001	0·585	0·638
6: invited at 24·5 years and school years 10-11	0·265	<0·001	0·239	0·293	0·244	<0·001	0·221	0·269	0·251	<0·001	0·227	0·277
7: not invited before age 24·5 and school year 8	0·031	<0·001	0·023	0·041	0·030	<0·001	0·023	0·040	0·032	<0·001	0·024	0·042
Jade Goody effect	1·408	<0·001	1·375	1·442	1·407	<0·001	1·374	1·441	1·411	<0·001	1·378	1·445
Age-by-cohort interactions												
CxA_25y_mixed_1	2·981	<0·001	2·755	3·226	2·981	<0·001	2·755	3·226	2·980	<0·001	2·754	3·224
CxA_25y_mixed_2	1·739	<0·001	1·631	1·855	1·742	<0·001	1·633	1·858	1·741	<0·001	1·632	1·858
CxA_25y_1	3·922	<0·001	3·712	4·145	3·952	<0·001	3·739	4·178	3·940	<0·001	3·729	4·164
CxA_25y_2	1·821	<0·001	1·728	1·918	1·837	<0·001	1·743	1·936	1·830	<0·001	1·736	1·928
CxA_24y5_1	2·912	<0·001	2·706	3·134	3·012	<0·001	2·797	3·244	2·974	<0·001	2·762	3·202
CxA_24y5_2	2·667	<0·001	2·539	2·801	2·745	<0·001	2·610	2·888	2·718	<0·001	2·587	2·856
Possible under-registration												
Jan 2006 - Dec 2017					1·000							
Jan 2018 - Sep 2018					1·009	0·480	0·985	1·033				
Oct 2018 - Mar 2019					1·136	<0·001	1·104	1·169				
Apr 2019 - Jun 2019					1·242	<0·001	1·197	1·289				
Awareness campaign									1·241	<0·001	1·202	1·281
Constant (baseline incidence rate)	6·31E-4	<0·001	6·05E-4	6·59E-4	6·19E-4	<0·001	5·93E-4	6·45E-4	6·24E-4	<0·001	5·98E-4	6·51E-4

Table S4: adjusted incidence rate ratios (IRRs) and 95% confidence intervals (CIs) of CIN3 in women aged 24.5 to <65 years.

	Model 1				Model 2				Model 3			
	IRR	**p**	**95% CI**		**IRR**	**p**	**95% CI**		**IRR**	**p**	**95% CI**	
Age (years)												
24·5 to <26	1·000				1·000				1·000			
26 to <30	0·952	0·005	0·919	0·985	0·952	0·005	0·919	0·985	0·952	0·005	0·920	0·985
30 to <35	0·625	<0·001	0·604	0·647	0·624	<0·001	0·603	0·646	0·624	<0·001	0·602	0·646
35 to <45	0·290	<0·001	0·280	0·300	0·289	<0·001	0·279	0·300	0·289	<0·001	0·279	0·300
45 to <55	0·091	<0·001	0·088	0·094	0·091	<0·001	0·088	0·094	0·091	<0·001	0·087	0·094
55 to <65	0·037	<0·001	0·035	0·038	0·037	<0·001	0·035	0·038	0·037	<0·001	0·035	0·038
Linear trend (drift)	0·991	<0·001	0·989	0·992	0·990	<0·001	0·989	0·992	0·989	<0·001	0·988	0·991
Seasonality												
Jan-Mar	1·000				1·000				1·000			
Apr-June	1·053	<0·001	1·038	1·068	1·048	<0·001	1·033	1·063	1·047	<0·001	1·032	1·062
July-Sept	1·043	<0·001	1·028	1·058	1·046	<0·001	1·030	1·061	1·046	<0·001	1·031	1·062
Oct-Dec	1·042	<0·001	1·026	1·057	1·038	<0·001	1·022	1·053	1·045	<0·001	1·030	1·061
Birth cohorts												
1: invited at age 20 years and no vaccine	0·796	<0·001	0·771	0·822	0·800	<0·001	0·774	0·826	0·802	<0·001	0·776	0·828
2: invited at age 20 or 25 years and no vaccine	0·857	<0·001	0·825	0·889	0·861	<0·001	0·829	0·893	0·863	<0·001	0·832	0·896
3: invited at age 25 years and no vaccine	0·906	<0·001	0·877	0·937	0·911	<0·001	0·881	0·943	0·914	<0·001	0·884	0·945
4: invited at age 24·5 years and no vaccine	1·000				1·000				1·000			
5: invited at 24·5 years and school years 12-13	0·655	<0·001	0·627	0·685	0·655	<0·001	0·626	0·685	0·652	<0·001	0·623	0·682
6: invited at age 24·5 and school years 10-11	0·362	<0·001	0·325	0·405	0·344	<0·001	0·308	0·385	0·342	<0·001	0·306	0·381
Jade Goody effect	1·438	<0·001	1·404	1·473	1·438	<0·001	1·404	1·473	1·440	<0·001	1·406	1·476
Age-by-cohort interactions												
CxA_25y_mixed_1	3·108	<0·001	2·872	3·363	3·105	<0·001	2·870	3·360	3·102	<0·001	2·867	3·357
CxA_25y_mixed_2	1·816	<0·001	1·703	1·938	1·815	<0·001	1·701	1·937	1·815	<0·001	1·701	1·937
CxA_25y_1	3·850	<0·001	3·642	4·069	3·849	<0·001	3·641	4·068	3·856	<0·001	3·649	4·076
CxA_25y_2	1·790	<0·001	1·699	1·886	1·790	<0·001	1·699	1·886	1·793	<0·001	1·702	1·890
CxA_24y5_1	2·453	<0·001	2·278	2·642	2·484	<0·001	2·305	2·676	2·499	<0·001	2·320	2·692
CxA_24y5_2	2·273	<0·001	2·170	2·381	2·298	<0·001	2·192	2·410	2·310	<0·001	2·204	2·421
Possible under-registration												
Jan 2006 - Dec 2017					1·000							
Jan 2018 - Sep 2018					0·950	<0·001	0·928	0·972				
Oct 2018 - Mar 2019					1·045	0·003	1·015	1·075				
Apr 2019 - Jun 2019					1·131	<0·001	1·090	1·173				
Awareness campaign									1·159	<0·001	1·122	1·196
Constant (baseline incidence rate)	5·21E-3	<0·001	4·99E-3	5·43E-3	5·18E-3	<0·001	4·96E-3	5·41E-3	5·13E-3	<0·001	4·92E-3	5·35E-3

Table S5: adjusted estimates of cohort-specific incidence rate ratios obtained from models using restricted cubic splines or categories for the age variable.

	Models with restricted cubic splines (RCS)						Categorical age		
	mkspline with knots(7)*			rcsgen with 8 user-specified knots**			7 age categories		
	Model 1	**Model 2**	**Model 3**	**Model 1**	**Model 2**	**Model 3**	**Model 1**	**Model 2**	**Model 3**
Invasive cervical cancer									
Birth cohorts									
1: invited at age 20 years and no vaccine	0·927	0·944	0·936	0·950	0·963	0·957	0·987	0·999	0·994
2: invited at age 20 or 25 years and no vaccine	0·990	1·007	0·999	1·053	1·067	1·061	1·077	1·090	1·084
3: invited at age 25 years and no vaccine	0·971	0·982	0·977	1·029	1·039	1·034	1·032	1·040	1·037
4: invited at age 24·5 years and no vaccine **(reference category)**	1·000	1·000	1·000	1·000	1·000	1·000	1·000	1·000	1·000
5: invited at 24·5 years and offered vaccine in school years 12-13	0·688	0·683	0·686	0·682	0·674	0·679	0·666	0·658	0·663
6: invited at 24·5 years and offered vaccine in school years 10-11	0·344	0·324	0·333	0·403	0·375	0·387	0·393	0·367	0·377
7: not invited before age 24·5 and offered vaccine in school year 8	0·139	0·133	0·142	0·291	0·277	0·295	0·129	0·125	0·131
CIN3									
Birth cohorts									
1: invited at age 20 years and no vaccine	1·051	1·069	1·061	1·037	1·049	1·044	0·965	0·977	0·973
2: invited at age 20 or 25 years and no vaccine	0·999	1·019	1·011	1·054	1·069	1·062	1·018	1·031	1·026
3: invited at age 25 years and no vaccine	0·973	0·988	0·982	1·036	1·049	1·043	1·005	1·018	1·013
4: invited at age 24·5 years and no vaccine **(reference category)**	1·000	1·000	1·000	1·000	1·000	1·000	1·000	1·000	1·000
5: invited at 24·5 years and offered vaccine in school years 12-13	0·613	0·607	0·610	0·605	0·597	0·601	0·614	0·609	0·611
6: invited at 24·5 years and offered vaccine in school years 10-11	0·229	0·210	0·218	0·266	0·240	0·250	0·265	0·244	0·251
7: not invited before age 24·5 and offered vaccine in school year 8	0·032	0·030	0·033	0·065	0·061	0·066	0·031	0·030	0·032

* RCS created using the mkspline Stata command with 7 knots placed at specific percentiles of the age variable as recommended by Harrell (2001).
** RCS created using the rcsgen command with 8 knots (internal knots: 22·5, 24·5, 26, 30, 40 and 50, boundary knots: min and max of the age variable) and orthogonalized with the Gram-Schmidt method.

Table S6: estimated cohort-specific cumulative incidence rates (CIRs) and 95% CIs for birth cohorts 4-7 obtained using models 1-3. Estimates were derived for women with diagnosis in January 2016 and all other covariates fixed at their reference values.

	Invasive cervical cancer			CIN3		
	Model1	**Model 2**	**Model 3**	**Model1**	**Model 2**	**Model 3**
	CIR (95% CI)	**CIR (95% CI)**	**CIR (95% CI)**	**CIR (95% CI)**	**CIR (95% CI)**	**CIR (95% CI)**
Birth cohort						
4: invited at age 24·5 yrs and no vaccine						
age 20 to <24·5 years	**9·6** (8·3, 11·0)	**9·4** (8·1, 10·7)	**9·6** (8·2, 10·9)	**284·1** (271·9, 296·3)	**278·3** (266·5, 290·2)	**280·7** (268·7, 292·8)
age 20 to <26 years	**50·3** (45·2, 55·4)	**49·8** (44·7, 54·8)	**50·1** (45·1, 55·2)	**1822·8** (1751·3, 1894·2)	**1809·1** (1737·8, 1880·4)	**1815·8** (1744·5, 1887·1)
age 20 to <30 years	**119·9** (109·5, 130·3)	**117·2** (106·9, 127·4)	**118·7** (108·4, 129·0)	**3582·7** (3473·2, 3692·2)	**3517·4** (3407·6, 3627·2)	**3544·1** (3434·7, 3653·4)
5: invited at age 24·5 yrs and offered vaccine in school years 12-13						
age 20 to <24·5 years	**6·4** (5·6, 7·3)	**6·2** (5·4, 7·1)	**6·3** (5·5, 7·2)	**174·5** (167·2, 181·8)	**169·4** (162·3, 176·5)	**171·6** (164·4, 178·8)
age 20 to <26 years	**33·5** (30·4, 36·7)	**32·7** (29·6, 35·9)	**33·2** (30·1, 36·4)	**1119·5** (1082·6, 1156·3)	**1101** (1063·3, 1138·6)	**1109·9** (1073·1, 1146·6)
age 20 to <30 years	**79·9** (72·7, 87·1)	**77·1** (70·0, 84·2)	**78·7** (71·5, 85·8)	**2200·4** (2133·9, 2266·8)	**2140·5** (2072·6, 2208·4)	**2166·2** (2100·7, 2231·7)
6: invited at age 24·5 yrs and offered vaccine in school years 10-11						
age 20 to <24·5 years	**3·8** (2·9, 4·7)	**3·5** (2·6, 4·3)	**3·6** (2·7, 4·5)	**75·2** (68·1, 82·3)	**67·9** (61·6, 74·2)	**70·4** (63·8, 76·9)
age 20 to <26 years	**19·8** (15·2, 24·3)	**18·3** (14·0, 22·5)	**18·9** (14·6, 23·2)	**482·4** (437·4, 527·5)	**441·1** (401·3, 481·0)	**455·1** (413·6, 496·5)
7: not invited before 24·5 yrs and offered vaccine in school year 8						
age 20 to <24·5 years	**1·2** (0·3, 2·2)	**1·2** (0·3, 2·1)	**1·2** (0·3, 2·2)	**8·8** (6·4, 11·3)	**8·4** (6·0, 10·7)	**8·9** (6·4, 11·3)

Table S7: Number of cases and 95% CIs that Models 1-3 estimate had been averted by June 2019 since the introduction of the HPV vaccination programme in England. These estimates were derived using the *margins* command in Stata.

	Number of prevented cases (95% CI)		
	Model 1	**Model 2**	**Model 3**
Invasive cervical cancer	436·4 (328·8, 544·0)	461·3 (351·3, 571·2)	447·6 (339·1, 556·1)
CIN3	16,778·1 (15,481·1, 18,075·0)	17,621·0 (16,280·8, 18,961·2)	17,235·4 (15,918·7, 18,552·1)